Application No.: 10/586,226 Docket No.: 313632002300

REMARKS

Claims 1-23, 25-27, 30-36 and 39 are pending in this application. Claims 25-27, 30-36 and 39 are withdrawn from consideration. Claims 1-23 are under examination and stand rejected. Careful consideration has been given to the grounds for rejection, and the following amendment and discussion are offered in response. Reconsideration is respectfully requested.

Restriction Requirement under 35 U.S.C. §§ 121 and 372

In response to the Restriction Requirement under 35 U.S.C. §§ 121 and 372, Applicants hereby confirm the provisional election of Group I, claims 1-23, made telephonically by Kate Murashige on 14 April 2010, without traverse.

Applicants expressly reserve their right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application, or an application claiming priority from this application.

The Rejections Under 35 U.S.C. § 102

Claims 1-3, 6-9, 12, 16, 17 and 19-23 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Langer, *et al.* (U.S. Patent No. 6,160,084). In particular, Langer's examples are said to disclose biocompatible and biodegradable multiblock copolymers composed of a crystallizable hard segment and a soft segment which the Examiner states is equivalent to the claimed pre-polymers, having a thermal transition temperature between room and body temperatures. Applicants respectfully traverse the rejections for at least the following reasons.

According to the Examiner, Langer, *et al.*, disclose block copolymers comprising hard segments of a polymer (PDS) prepared from p-dioxanone and ethylene glycol, and soft segments of either poly(ε-caprolactone)diol (PCL), or a polymer (PLCG) prepared from dilactide, diglycolide, and ethylene glycol. The Examiner is of the opinion that the polymers of Langer, *et al.*, are amorphous at physiological conditions, since these polymers have a T_g below 37°C (Langer, *et al.*,

column 16, Table 5). This T_g is explicitly mentioned in Table 5 of Langer, *et al.*, for PDL23 and PDL30.

Applicants respectfully disagree that these polymers are amorphous under physiological conditions. Instead, the block copolymers of Langer, *et al.*, are semi-crystalline, because they comprise the semi-crystalline p-dioxanone segments that have a melting temperature T_m above body temperature (Langer, *et al.*, column 14, Table 1). The melting temperature is preserved in the block copolymer, as is shown in Table 5 of Langer, *et al.*, for polymers PDL30, PDC27, PDC31, and PDC40.

For the other polymers in Table 5, the Examiner refers to the Fox equation (Sheet 1) and calculates values to show that the T_g of these polymers is also below 37°C. However, the Examiner ignores the fact that the Fox equation requires perfect mixing and is inapplicable when the copolymer comprises a semi-crystalline segment.

Table 5 of Langer, *et al.*, does not mention a melting temperature for PDL23 and PDC22. There polymers are, however, inherently crystalline, because they are shape-memory polymers. According to claim 1 of Langer, *et al.*, the shape-memory polymers have one hard and one soft segment for non-crosslinked and non-blended systems, which implies the presence of at least two phase transitions. The phase transition of the hard segment is at least 10°C above the phase transition of the soft segment (see, e.g., Langer, *et al.*, column 3, lines 7-10).

Table 2 in column 15 of Langer, *et al.*, shows that the hard segment for PDL23 is PDS1200, while the soft segment is PLGA2000. Similarly, the hard segment for PDC22 is PDS1200, while the soft segment is PCL2000.

Under "*Synthesis of Thermoplastic Elastomers (Multiblock Copolymer)*" in column 14, Langer, *et al.*, state that the T_{trans} for the soft segments for PDC polymers is the melting point of poly(ε-caprolactone) (Langer, *et al.*, column 14, lines 62-63). From this disclosure it follows that T_{trans} of the hard segment of PDC22 must be the melting temperature of PDS1200, which is 95°C (Langer, *et al.*, column 14, Table 1), well above body temperature.

Similarly, for PDL polymers Langer, *et al.*, state that the T_{trans} of the soft segment is the glass transition point of α,ω-dihydroxy [oligo(L-lactate-co-glycolate) ethylene oligo(L-lactate-co-glycolate)] segment (Langer, *et al.*, column 14, lines 64-67). From this disclosure it follows that T_{trans} of the hard segment of PDL23 must be the melting temperature of the PDS1200, which is 95°C (Langer, *et al.*, column 14, Table 1), well above body temperature.

Moreover, while T_{trans} of the hard segment is not noted for PDL23 in Table 5 in column 16 of Langer, *et al.*, Table 11 in column 17 referring to the same PDL23 polymer shows that this polymer does have shape-memory properties, thereby indicating that PDL23 must have a crystalline hard segment of PDS1200.

Most likely, the lack of a T_m value in Langer, *et al.*, column 16, Table 5 is due to the applied Differential Scanning Calorimetry (DSC) method which has been used by Langer, *et al.* It is common knowledge for the person of ordinary skill in the art that the degree of crystallinity is very dependent on the applied cooling rate. At too high cooling rate, the polymer may not have time to crystallize, since crystallization is a kinetically controlled process. When the cooling rate is too high, upon reheating no melting point is detected, while at a lower cooling rate the melting point may be detected upon reheating. Especially for polymers containing a low degree of crystallizable segments, a slow cooling rate is important to allow the polymer chains sufficient time for crystallization. Also, at low degrees of crystallinity, a highly sensitive DSC method is recommended, such as modulated DSC, which may be able to detect small thermal transitions where normal DSC cannot.

In addition, the invention of Langer, *et al.*, is directed to materials that are used in the body. Importantly, for use in the body, the shape-memory materials must have a T_{trans} of the hard segment under physiological conditions, to enable retainment of the memorized shape in the body. In contrast, the multiblock copolymers of the present invention do not have any phase transition under physiological conditions - they are amorphous.

Moreover, Landlein & Langer have disclosed that the same PDC multiblock copolymers have a T_m of the PDS segment at a PDS content as low as 10 wt.%. See, e.g., Landlein & Langer,

Science (2002) 296:1673-1676, at Figure 1 (copy enclosed as Exhibit A). Although the length of the PDS and PCL segments is not mentioned in this publication, the results indicate that the PDC multiblock copolymers are indeed semi-crystalline.

The test for anticipation is one of strict identity. *Trintec Industries. Inc. v. Top-U.S.A. Corp.*, 63 USPQ.2d 1597 (Fed. Cir. 2002). In view of the foregoing remarks, Applicants respectfully submit that the invention as claimed is not anticipated by Langer, *et al.*, which fails to disclose multi-block copolymers that are amorphous at physiological conditions.

Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

The Rejections Under 35 U.S.C. § 103

Claims 4, 5, 10, 11, 13, 14 and 18 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Langer, *et al.*, as applied to claim 1, as evidenced by Sheet 2 (Lactide pricing information, Alfa Aesar). Claims 4 and 13-15 stand further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Langer, et al. in view of Rashkov, *et al.* (*Macromolecules*, 1996, pp 55-56). Applicants respectfully traverse the rejections for at least the following reasons.

The Examiner acknowledges that Langer, *et al.* do not disclose all the limitations of these claims, but takes the position that one of skill in the art would have a reasonable expectation that the modified copolymers would posses T_g values similar to Langer's examples and would be amorphous under physiological conditions. Rashkov, *et al.* is cited as disclosing the use of PEG as an initiator for ring-opening polymerization and the Examiner asserts that it would be obvious to use the PEG/PLA copolymers of Rashkov, *et al.* as segments in the polymers of Langer, *et al.*

The present invention claims multiblock copolymers for use in the body that are completely amorphous under physiological conditions. This is in contrast to the polymers described by Langer, *et al.*, which, as discussed above, have crystalline segments at body temperature (acting as physical cross-links to maintain the memorized shape), and are not amorphous.

As noted in the memorandum from the Deputy Commissioner, issued immediately in response to the *KSR* decision, in formulating a rejection for obviousness based on a combination of elements, it remains necessary to identify a reason why a person of ordinary skill in the art would have combined the prior art elements "in the manner claimed." In addition, if a proposed modification would render the prior art unsatisfactory for its intended purpose or would change its principle of operation, then there is no suggestion or motivation to make the proposed modification and the claims are not *prima facie* obvious. *See* MPEP § 2143.01(V)-(VI).

As already discussed, Langer, *et al.* is directed to shape-memory materials for use in the body. Such materials must have a T_{trans} of the hard segment under physiological conditions such that the memorized shape is retained in the body. By comparison, the multiblock copolymers of the present invention do not have any phase transition and are amorphous under physiological conditions.

Applicants respectfully submit that one of skill in the art would have had neither a motivation to modify Langer, *et al.*'s polymers to make them amorphous, nor a reasonable expectation of success, because such amorphous materials wouldn't reasonably be expected to be useful as shape-memory materials in the body. Accordingly, the skilled person would have no motivation to practice the invention as claimed in view of Langer, *et al.*'s disclosure, taken as a whole. In addition, modification of Langer, *et al.*'s polymers to make them amorphous would render them unsuitable for their intended purpose.

In view of these differences, Applicants respectfully submit that the invention as claimed in claims 4, 5, 10, 11, 13, 14 and 18 cannot be considered obvious over Langer, *et al.*

With regard to the rejection of claims 4 and 13-15 over Langer, *et al.* in view of Rashkov, *et al.*, Applicants respectfully note that, as discussed in detail above, independent claim 1 (from which claims 4 and 13-15 directly or indirectly depend) is nonobvious over the Langer, *et al.* The Examiner has pointed to nothing in Rashkov, *et al.* that addresses the fundamental deficiencies in the Office's *prima facie* case of obviousness over Langer, *et al.* alone. Accordingly, the claimed

invention cannot be considered obvious over Langer, *et al.* or Rashkov, *et al.*,, alone or in combination.

The amorphous multiblock copolymers of the present invention are especially suitable for drug delivery. The polymer matrix is rubbery under body conditions. Under these conditions, the polymer matrix is permeable to high molecular weight drugs and to the degradation products that are released, thereby preventing the generation of an acidic environment. Also, the phase transition below body temperature at physiological conditions make these polymers very suitable as an implant in the body as they soften under physiological conditions and give favorable interactions with the surrounding tissue and lower the chance on tissue irritation as compared to rigid implants.

Moreover, the materials of the present invention allow processing at relatively low temperatures, thus avoiding trans-esterification and other side-reactions that may cause the generation of undesired degradation and other by-products.

With regard to Gorna, *et al.*, which is made of record but not relied upon in the present Office Action, the Applicants respectfully note that Gorna, *et al.*'s multiblock copolymers are prepared by reacting a macrodiisocyanate (referred to as prepolymer) with a diol, inherently resulting in an alternating block copolymer.

In view of the foregoing remarks, Applicants respectfully submit that the invention as claimed is not obvious over Langer, *et al.*, alone or in combination with Rashkov, *et al.* Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

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CONCLUSION

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 313632002300.

Respectfully submitted,

Dated: August 20, 2010 By: 

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FEE SUMMARY SHEET

Office Action

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